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Prediction of atrial fibrillation recurrence after cardioversion in patients with left-atrial dilation

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Abstract

Aims Little is known about the impact of left-ventricular (LV) diastolic dysfunction on risk of atrial fibrillation (AF) recurrence in patients with left-atrial (LA) dilation. To evaluate, in patients with symptomatic persistent AF and LA dilation, the incremental role of LV diastolic dysfunction in predicting early AF recurrence after cardioversion (CV).

Methods and results From July 2011 to July 2013, 175 patients with persistent AF referred to our centre for CV were screened. Inclusion criteria were: European Heart Rhythm Association (EHRA) class ≥2 despite optimal medical treatment and heart rate at rest ≤80 bpm, LA volume ≥34 mL/m^2, EF > 35%, absence of untreated ischaemic disease and significant valvular disease, successful CV. Finally, 127 patients (age 64 ± 10 years, 60% EHRA ≥3, LA volume 42 ± 15 mL/m^2) were enrolled. At 3 months, 37 (29%) patients presented AF recurrence. At univariate analysis, AF duration >90 days before CV (*P* < 0.01), septal e' <8 cm/s (*P* 0.03), and septal E/e' ratio ≥11 (*P* < 0.001) but no LA dimensions significantly correlated with AF recurrence. Logistic regression analysis confirmed septal E/e' ratio ≥11 as the best predictor of recurrence (OR 3.25 95% CI 1.19–8.86 *P* 0.001) together with an AF duration >90 days before the CV (OR 2.69 95% CI 1.01–7.53 *P* 0.04). At ROC curve analysis, the septal E/e' ratio ≥11 showed the best diagnostic accuracy (AUC 0.66, 95% CI 0.55–0.76, *P* 0.007).

Conclusion In this population with symptomatic persistent AF and LA enlargement, septal E/e' ratio ≥11 and AF duration >90 days predicted AF recurrence at 3 months.

Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance encountered in clinical practice.[1]

Restoration of sinus rhythm (SR) may relieve symptoms and improve left-ventricular (LV) function. AF cardioversion (CV) is a potentially efficient treatment, in some cases the procedure is resolutive and in others is a valid bridge procedure to ablation or pharmacological therapy of rate control.[2] Nevertheless, AF recurrence after CV remains common despite the use of potent anti-arrhythmic drugs.[3]

Before CV is pivotal to determine the procedure's success, thereby, procedure-related risk may be avoided and cost-effectiveness may be improved.

Several echocardiographic variables detected before the restoration of SR have been reported to predict AF recurrence in patients after successful CV but their role is still unclear.[4] In particular, left atrial (LA) volume is a significant and independent predictor of AF recurrence,[5] but may underperform in the presence of severe LA enlargement. Tissue Doppler imaging of mitral annulus motion has been extensively used to explore LV performance. Current guidelines of the American Society of Echocardiography propose a ratio between the early diastolic transmitral flow velocity (E wave) and the septal early diastolic mitral annular velocity (e' wave) ≥11 as a predictor of elevated LV filling pressure[6] in course of AF. The septal E/e' ratio has been demonstrated to be the best echocardiographic predictor of AF recurrence at 3 months in an unselected population of patients who underwent catheter ablation[7] nevertheless there is a lack of knowledge about the prognostic role of this parameter in patients with LA enlargement who underwent CV.

Considering this assumption, the aim of this monocentric prospective study was to evaluate the impact of LV diastolic dysfunction on the risk of AF recurrence in a selected population with symptomatic AF and moderate-to-severe LA enlargement and to compare it with other echo-Doppler and clinical predictors.

Methods

Study population

A total of 175 patients with persistent AF referred to our Cardiology Division submitted to a direct-current CV between July 2011 and July 2013 were screened. Inclusion criteria were: European Heart Rhythm Association (EHRA) class ≥2 despite optimal medical treatment and heart rate at rest ≤ 80 bpm, moderate-to-severe LA enlargement[8] (LA volume ≥34 mL/m^2), ejection fraction (EF) >35%, and successful CV. Exclusion criteria were: presence of untreated ischaemic disease (defined as ≥1 of the following: any symptom of angina, new segmental wall motion abnormalities, or positive exercise stress test's result), significant valvular disease (valvular stenosis of any degree, moderate or severe valve regurgitation, valvular prosthesis), acute pericarditis and/or constrictive pericarditis, acute myocarditis, congenital heart disease, permanent pacing, all types of surgery within 3 months, patients on amiodaron treatment and prior AF ablation. From the baseline population, we selected and analysed 127 patients who met the inclusion criteria.

Clinical and echocardiographic data were collected immediately before CV and were also registered the antiarrhythmic therapy set at discharge. Primary outcome was the early (at 3 months) recurrence of AF.

Clinical data

Clinical data obtained before CV included age, sex, body mass index (BMI), hypertension, diabetes mellitus, dyslipidaemia, smoking status, medical history of coronary artery disease or of dysthyroidism, pharmacological treatment, duration of the AF before CV, and previous episode(s) of AF. In particular, hypertension, diabetes mellitus, dyslipidaemia and smoking were defined according to the latest European guidelines.[9]

Moreover, glomerular filtration rate was evaluated and estimated from Cockroft-Gault formula.

Concerning the therapy before the CV, we enrolled patients in optimal heart rate control with a baseline heart rate ≤80 bpm as suggested in the latest European Guidelines[10] and we also assessed for each patient the AF- related symptoms at the enrolment with the EHRA score.[10] Moreover, the HASBLED and CHA2DS2-VASc score were registered according to the current European guidelines on AF.[2]

According to AF duration, all patients were stratified into two categories: group 1 included patients with AF lasting ≤90 days before CV and group 2 included patients with AF lasting >90 days.

Restoration of SR was performed through electrical CV. During electrical CV, patients were under adequate general sedation and oxygen saturation, electrolytes and anticoagulation status were monitored. All direct-current CVs were performed using biphasic defibrillator with energy selected on 200 Joules.

After conversion to SR, patients received optimal medical prophylactic therapy including class Ic/III antiarrythmic drugs with the exception of amiodaron, according to the latest ESC guidelines on AF.[2] The decision to prescribe antiarrhythmic prophylaxis was taken after an accurate global evaluation of risk of AF relapse by an investigator blinded to results of tissue Doppler assessment. Treatment with non-antiarrhythmic cardiovascular agents was kept unchanged in all patients. All patients received appropriate oral anticoagulation 3 weeks before and 4 weeks after electrical CV. All patients were then followed one time a week for the first month and then had monthly visits until 3 months after CV. A targeted clinical

examination and a 12-lead electrocardiogram were performed at each visit. A 24 h ambulatory electrocardiographic monitoring was performed in all patients who were in SR at 3-month follow-up.

Echocardiographic evaluation

A complete transthoracic echocardiographic evaluation was performed with a Philips IE33 Echocardiographic system (Royal Philips Electronics, Amsterdam, The Nederlands). Echocardiographic evaluations included M mode, 2D and Doppler evaluation, performed according to current guidelines.[6,8] Moreover, 44 patients (34%), because of an inadequate coagulation before CV, underwent a transoesophageal echocardiogram (TEE) to exclude the presence of thrombi in the left-atrial appendage.

M-Mode evaluation and 2D evaluation

LA anterior–posterior, superior–inferior diameters were measured on the parasternal long-axis and apical 4-chamber views at end-systole, according to the American Society of Echocardiography (ASE) guideline.[8] The LA end-systolic volume (LAESV), LA end-diastolic volume (LAEDV) were assessed by the Simpson's method from the apical 4- and 2-chamber views. The measurements of the LA dimensions and volumes were calculated by averaging data obtained in 10 consecutive beats. The total left-atrial emptying fraction (LAEF) were calculated with the formula (LA maximum volume-LA minimum volume)/LA maximum volume×100 and the left-atrial expansion index (LAEI) were obtained with the formula: (LAmaximumvolume−LAminimumvolume)/LAminimumvolume×100.

[11] LV volume and the ejection fraction (EF) were assessed by Simpson's method. The LV mass were assessed in parasternal long-axis view with M-Mode with the formula[8]: LVmass=0.8×{1.04[(LVIDd + PWTd + SWTd)3−(LVIDd)3]}+0.6g,

where LVDd is the LV diastolic diameter and PWTd and SWTd are posterior wall thickness at end diastole and septal wall thickness at end diastole, respectively.

Doppler evaluation

Transmitralic pulsed Doppler was recorded from the apical 4-chamber view, with the sample volume positioned between the tips of the mitral leaflets. The early diastolic transmitral flow velocity (E wave) and the E-wave deceleration time (DT) were measured. Pulsed tissue Doppler imaging (TDI) of mitral annulus motion were performed from the apical 4-chamber view by placing a 5 mm sample volume at the junction between the basal lateral and septal myocardium and the adjacent mitral annulus. Septal and lateral early (e' wave) diastolic mitral annular velocities were recorded and consequently the ratio between the E wave and the septal and the lateral e' was calculated. e' was used as a relatively preload-independent measurement of LV relaxation, and E/e' ratio, was assumed as an index of LV filling pressure.[12] A DT <150 ms, a septal e' wave <8 cm/s and a septal E/e' ratio ≥11 were considered as cut off for increased LV filling pressures.[6,12] Moreover, we also collected the peak ejection velocity (lateral s' wave).

Pulmonary venous flow pattern (S and D waves) was collected in the apical 4-chamber view and lastly the pulmonary artery systolic pressure (sPAP) was also recorded.

In patients who underwent TEE, LA appendage anterograde flow velocity with Pulsed Doppler[13] was recorded and analysed.

All measurements were calculated by averaging data obtained in 10 consecutive beats.

Speckle tracking

A 4-chamber 2D image was collected for 58 patients (46%) before the CV for speckle-tracking evaluation. Echocardiographic images were stored in digital cineloop format (frame rate between 70 and 100 frames per second) for off-line analysis by customized 2D QLAB software that employs strain rate echocardiographic technology for angle-independent measures of 2D strain. To quantify the LA global deformation, we subdivided the LA in six equidistant regions and, taking as a reference point the QRS onset, we measured the positive peak atrial longitudinal strain.[14]

Reproducibility

Reproducibility of echo-Doppler measurements in our laboratory was previously reported.[15] For this study, variability was assessed in a randomly selected subset of 20 patients. Intraobserver coefficients of variation were 3.1 and 3.5% for septal and lateral e' and 3.5 and 3.8% for septal E/e' ratio and lateral E/e' ratio, respectively. Corresponding intraclass correlation coefficients were all included between 0.96 and 0.98 ($P < 0.001$). Interobserver coefficients of variation were 6.5% for septal e' and 7.2% for septal E/e' ratio, with corresponding intraclass correlation coefficients of 0.94 and 0.93, respectively ($P < 0.001$ for the two comparisons).

Predefined parameters of AF recurrence

Predefined clinical and echo-Doppler parameters studied as risk factors of AF recurrence after CV are shown in *Table 1*.

Table 1. Predefined clinical, therapeutic, and echocardiographic parameters studied as risk factors for AF recurrence

Parameter	Risk value
Age[16]	>70 years
AF duration[17]	>90 days
Previous CV[18]	Yes
CAD[19]	Absence
Antiarrythmic drugs (Ic/III class)[20]	Absence
RAAB[21]	Absence
EF	<55%
Pulmonary venous systolic flow[17]	<35 cm/s
Septal e'[12]	<8 cm/s
Septal E/e' ratio[12]	≥11
DT[6]	<150 ms

AF, atrial fibrillation; CV, cardioversion; CAD, coronary artery disease; RAAB, renin–angiotensin–aldosterone system's blockers; EF, ejection fraction; DT, deceleration time.

Statistical methods

Continuous variables are expressed as mean ± standard deviation; categorical variables are presented as counts and percentages of the respective strata. An univariate model, based on prespecified variables, was made to detect predictors of AF recurrence with the Student's *t*-test or χ^2 test for the continuous and non-continuous variables, respectively. To test the independent correlation of these parameters with the composite endpoint, all variables reporting a significant correlation, set to $P \leq 0.1$, at univariate analysis were included in a stepwise multivariate logistic regression model. Receiver-operated characteristic (ROC) curve was produced and the area under the curve was calculated to test the ability of the parameters for the prediction of AF recurrence. Younden's index was used to find the value with best sensitivity and specificity. Significance was set at $P < 0.05$. All statistical analyses were performed with the program package SPSS.

Results

Clinical and echo-Doppler characteristics

Clinical and echocardiographic characteristics of the study population (127 patients) are shown in *Tables* 2 and 3.

Table 2. Clinical characteristics at baseline and comparison between patients with and without AF recurrence at 3 months from CV

	Study population *n* = 127	**No AF recurrence *n* = 90 (71%)**	**AF recurrence *n* = 37 (29%)**	**OR (95% CI)**	***P*-value**
Males, *n* (%)	98 (77)	70 (77)	28 (76)	0.88 (0.36–2.2)	0.79
Ages (years)	64 ± 10	64 ± 15	65 ± 10	—	0.67
BMI (kg/m^2)	19 ± 1.7	18 ± 1.5	19 ± 2	—	**0.002**
HR (bpm)	73 ± 13	74 ± 14	70 ± 10	—	0.12
eGFR (mL/min)	74 ± 21	77 ± 22	71 ± 29	—	0.2
Smokers, *n* (%)	17 (13)	11 (12)	6 (16)	1.3 (0.4–4)	0.55
Hypertension, *n* (%)	84 (66)	61 (68)	23 (62)	0.78 (0.3–1.7)	0.54
Diabetes mellitus, *n* (%)	7 (5)	5 (5)	2 (5)	0.97 (0.1–5.1)	0.98
Dyslipidaemia	39 (30)	25 (28)	14 (38)	1.5 (0.6–3.5)	0.27
CAD, *n* (%)	9 (7)	8 (8)	1 (3)	0.28 (0.01–1.8)	0.24
Dysthyroidism, *n* (%)	19 (15)	13 (14)	6 (16)	1.1 (0.3–3.2)	0.78
Stroke, *n* (%)	5 (4)	4 (4)	1 (3)	0.59 (0.02–4.9)	0.71
EHRA class II, *n* (%)	51 (40)	35 (39)	16 (43)	1.1 (0.5–2.6)	0.65
EHRA class III–IV, *n* (%)	76 (60)	55 (61)	21 (56)	0.8 (1.3–1.8)	0.65
Previous CV, *n* (%)	55 (43)	38 (42)	17 (46)	1.1 (0.5–2.5)	0.70
Beta-blockers, *n* (%)	56 (44)	38 (42)	18 (48)	1.2 (0.59–2.8)	0.51
Antiarrhythmic drugs (Ic/III class) , *n* (%)	74 (58)	49 (54)	25 (67)	1.7 (0.7–3.9)	0.17
RAAB, *n* (%)	58 (45)	43 (48)	15 (40)	0.7 (0.3–1.6)	0.46

AF, atrial fibrillation; BMI, body mass index; CV, cardioversion; HF, heart rate, eGFR, glomerular filtration rate estimated from Cockroft-Gault formula; CAD, coronary artery disease; EHRA, European Heart Rhythm Association; RAAB, renin–angiotensin–aldosterone system's blockers. The significant *P*-values <0.05 are denoted in bold.

Table 3. Echo-Doppler parameters at baseline and comparison between patients with and without AF recurrence at 3 months from CV

	Study population *n* = 127	**No AF recurrence *n* = 90 (71%)**	**AF recurrence *n* = 37 (29%)**	***P*-value**
AP left atrium diameter (mm)	46.3 ± 8.3	45.6 ± 10.3	47.5 ± 10.3	0.28
SI left atrium diameter (mm)	61 ± 8.1	60.9 ± 8.5	62.1 ± 7.4	0.45
Maximum LA area (cm^2)	25.3 ± 5	24.8 ± 5.6	26.5 ± 4.4	0.10
Maximum LA volume (mL)	80 ± 28.8	81.3 ± 33.6	83.6 ± 25.6	0.70
Indexed maximum LA volume (mL/m^2)	42 ± 15	43.3 ± 17.5	44 ± 14	0.82
Total LA emptying fraction (%)	25 ± 13	25 ± 14	25 ± 13	0.99

	Study population *n* = 127	No AF recurrence *n* = 90 (71%)	AF recurrence *n* = 37 (29%)	*P*-value
LA expansion index (%)	37 ± 26	37 ± 26	38 ± 27	0.89
EF (%)	60 ± 6.8	59 ± 6	61 ± 7	0.10
LV mass (g)	240.6 ± 83.4	223.9 ± 73.4	250.9 ± 91.2	0.10
Lateral s' (cm/s)	7.9 ± 2.27	7.7 ± 2.3	7.8 ± 2.2	0.82
E wave (cm/s)	91 ± 26	87 ± 19	95 ± 27	0.06
DT (ms)	184 ± 62	181 ± 66	189 ± 59	0.52
Septal e' (cm/s)	9.6 ± 2.4	10.1 ± 2.8	8.9 ± 1.4	**0.01**
Lateral e' (cm/s)	13 ± 3	13.4 ± 3.4	12.7 ± 2.6	0.26
Average e' (cm/s)	10.7 ± 2.8	11.7 ± 2.6	10.5 ± 2	**0.01**
Septal E/e' ratio	9.9 ± 4.9	9.2 ± 4	11 ± 4.2	**0.02**
Lateral E/e' ratio	7.5 ± 3.5	7 ± 2.6	7.8 ± 2.7	0.12
S wave (cm/s)	43 ± 15	45 ± 17	41 ± 13	0.20
D wave (cm/s)	57 ± 17	55 ± 18	60 ± 16.6	0.14
sPAP (mmHg)	30.3 ± 9	28.8 ± 11	32.7 ± 8.2	**0.05**
LA appendage anterograde flow velocity (cm/s)[a]	50 ± 21	56 ± 21	43 ± 21	**0.04**
LA global longitudinal strain (%)[b]	4 ± 7.4	5 ± 9	1.6 ± 13	0.41

AP, antero-posterior; SI supero-inferior; LA, left atrial; CV, cardioversion; EF, ejection fraction; LV, left ventricular; DT, deceleration time; sPAP, pulmonary artery systolic pressure. [a]Data available for 44 patients. [b]Data available for 58 patients. The significant *P*-values <0.05 are denoted in bold.

Ninety-eight patients (77%) were males and the average age was 64 ± 10 years. The majority of patients suffered from hypertension (66%), 5% had diabetes, and 7% had history of coronary artery disease; 76 patients (60%) were highly symptomatic due to AF (EHRA class ≥3) and 55 (43%) were subjected to a previous CV. Average CHA_2DS_2 –VASc score was 2.5 and average HASBLED score was 1. Patients enrolled in the study showed a good systolic function (EF 60 ± 6.8%) with a moderate-to-severe LA enlargement (indexed LA volume 42 ± 15 mL/m^2, antero-posterior LA diameter 46.3 ± 8.3 mm).

According to AF duration before CV, we obtained two groups: group 1 with 81 patients (64%) with AF lasting ≤90 days before CV and group 2 with 46 patients (36%) with AF lasting more than 90 days. The two prespecified groups did not show any significant difference among clinical and echo-Doppler parameters.

At discharge, all patients received oral anticoagulant therapy and 99 patients (78%) received an antiarrhythmic prophylaxis.

Predictors of atrial fibrillation recurrence after CV

After 3 months of follow-up, 37 patients (29%) presented a recurrence of AF, 17 patients (21%) in group 1 (AF lasting ≤90 days) and 20 patients (43%) in group 2 (AF lasting >90 days).

Patients with AF recurrence at follow-up showed a higher BMI without other significant difference among the clinical variables (*Table 2*).

Univariate analysis concerning the echocardiographic parameters are shown in *Table 3*. Patients with AF recurrence at 3 months showed lower septal e' velocity (respectively, septal e' velocity 8.9 ± 1.4 vs. 10.1 ± 2.8 cm/s, *P* 0.01) and higher septal E/e' ratio (respectively, 11 ± 4.2 vs. 9.2 ± 4, *P* 0.02) when compared with patients who remained in SR with a trend towards higher sPAP (32.7 ± 8.2 vs. 28.8 ± 11 mmHg, *P* 0.05). Moreover, in patients who did not maintain the SR was pointed out a lower LA appendage anterograde flow velocity (43 ± 21 vs. 56 ± 21 cm/s, *P* 0.04). No significant difference in LA volume and dimensions was

detected between patients with and without AF recurrence or in the lateral E/e' ratio. At univariate analysis of predefined predictors of AF recurrence (*Table 4*), patients with AF duration more than 90 days before CV had a risk of AF recurrence about 3 times greater (OR 2.9 95% CI 1.3–6.4 *P* < 0.01) when compared with patients with AF lasting for less than 90 days. Moreover, using the predefined cut off, patients with a septal e' <8 cm/s or with septal E/e' ratio ≥11 had, respectively, a risk of AF recurrence of 3 times (OR 2.9 1.08–8 *P* 0.03) and 6 times (OR 6.7, 95% CI 2.6–18.1; *P* < 0.001) greater. At the logistic regression analysis (*Table 5*) including the clinical and echocardiographic variables, the septal E/e' ratio ≥11 was confirmed as the best predictor of events (OR 3.25 95% CI 1.19–8.86 *P* 0.001), together with the AF duration before CV >90 days (OR 2.69 95% CI 1.01–7.53 *P* 0.04). Moreover, the sPAP would seem to be related to a lower risk of AF recurrence (OR 0.86 95% CI 0.78–0.93 *P* 0.001). At ROC curve analysis (*Figure 1*), a septal E/e' ratio ≥8 showed the best sensitivity (89%), whereas a septal E/e' ratio ≥11 had the best specificity (85%) to predict AF recurrence at 3 months and moreover septal E/e' ratio ≥11 presented the best diagnostic accuracy (AUC 0.66, 95% CI 0.55–0.76 *P* 0.007). Younden's index confirmed E/e' ratio ≥11 a better cut-off than ≥8 (respectively, 0.32 vs. 0.26). The combination of AF duration >90 days and septal E/e' ratio ≥11 in a 2-point score (*Figure 2*) showed the best diagnostic accuracy (AUC 0.70, 95% CI 0.59–0.80 *P* 0.003), whereas the LA volume did not show any significant diagnostic accuracy in the prediction of AF recurrence (AUC 0.56, 95% CI 0.45–0.67 *P* 0.34).

Table 4. Comparison of clinical and echocardiographic prespecified variables in patients with or without AF recurrence at 3 months from CV

	Not AF recurrence *n* = 90 (71%)	**AF recurrence *n* = 37 (29%)**	**OR (95% CI)**	***P*-value**
Age >70 years, *n* (%)	27 (30)	12 (32)	1.1 (0.4–2.5)	0.39
AF duration before CV >90 days, *n* (%)	26 (29)	20 (54)	2.9 (1.3–6.4)	**<0.01**
Previous CV, *n* (%)	38 (42)	17 (46)	1.1 (0.5–2.5)	0.70
Absence of CAD, *n* (%)	82 (92)	36 (97)	3.4 (0.5–80)	0.24
Absence of antiarrythmic drugs (Ic/III class) , *n* (%)	20 (22)	8 (22)	1.0 (0.39–2.70)	1.0
Absence of RAAB, *n* (%)	47 (52)	22 (60)	1.3 (0.6–2.9)	0.46
EF <55%, *n* (%)	8 (8)	5 (13)	1.5 (0.4–5.3)	0.22
S wave <35 cm/s, *n* (%)	15 (16)	10 (27)	1.84 (0.7–4.6)	0.19
Septal e' <8 cm/s, *n* (%)	10 (11)	10 (27)	2.9 (1.08–8)	**0.03**
Septal E/e' ratio ≥11, *n* (%)	9 (10)	16 (43)	6.7 (2.6–18.1)	**<0.001**
DT <150 ms, *n* (%)	22 (24)	13 (35)	1.6 (0.7–3.8)	0.11

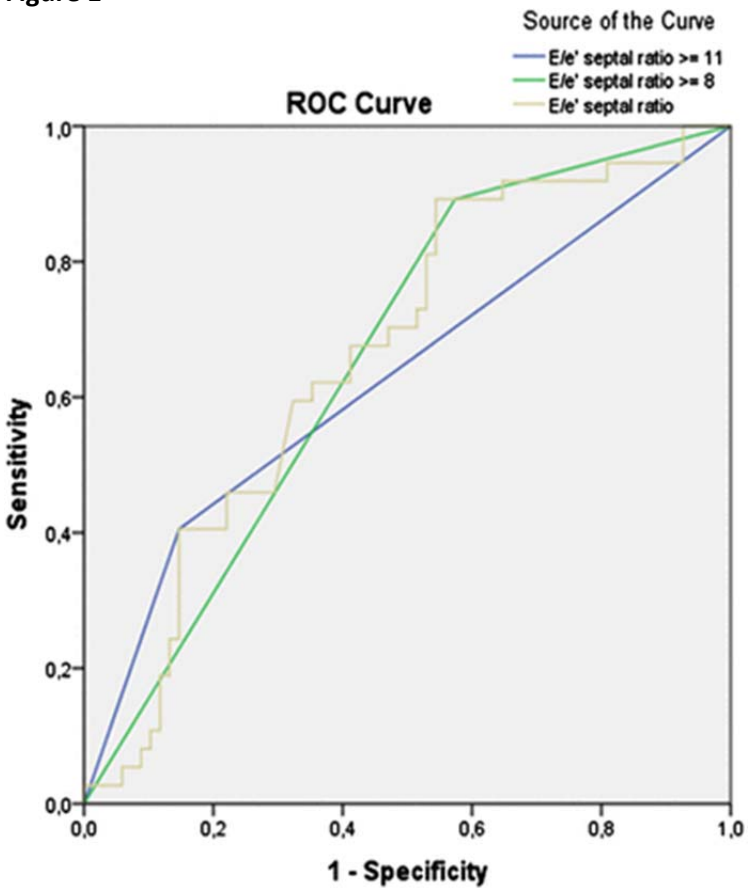
AF, atrial fibrillation; CV, cardioversion; CAD, coronary artery disease; RAAB, renin–angiotensin–aldosterone system's blockers; EF, ejection fraction; DT, deceleration time. The significant *P*-values <0.05 are denoted in bold.

Table 5. Multivariate analysis of candidate predictors of AF recurrence at 3 months

	OR	**Lower CI (95%)**	**Upper CI (95%)**	***P*-value**
BMI (kg/ m^2)	1.15	0.95	1.40	0.16
AF duration before CV >90 days	2.69	1.01	7.53	**0.04**
Maximum LA area (cm^2)	1.00	0.89	1.13	0.91
LV mass (g)	1.02	0.99	1.01	0.25
Septal e'<8 cm/s	1.27	0.22	7.20	0.78
Septal E/e' ratio ≥11	3.25	1.19	8.86	**0.001**
sPAP (mmHg)	0.86	0.78	0.93	**0.001**

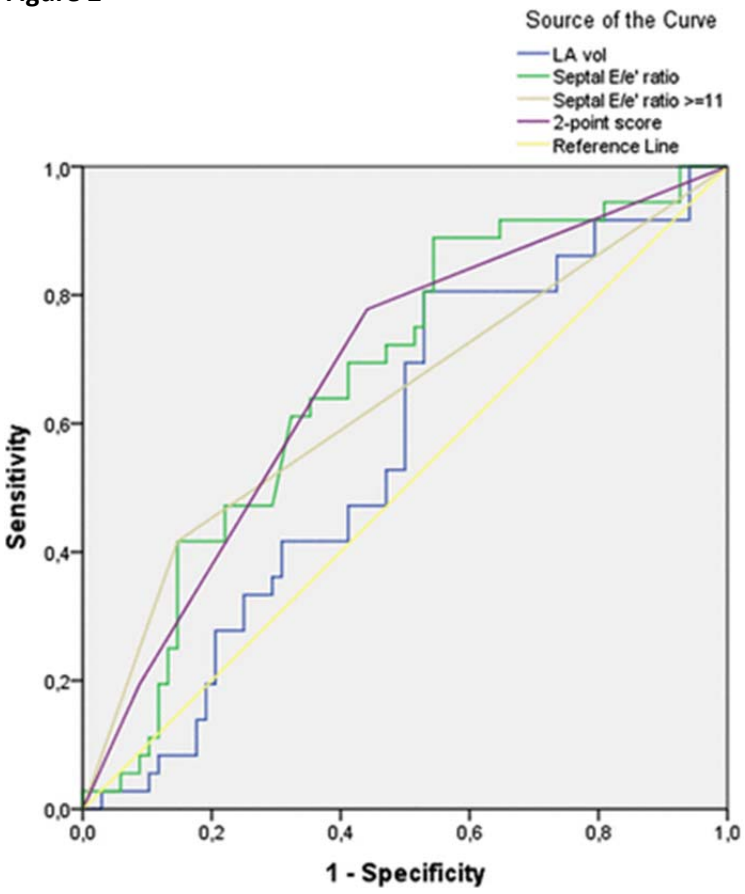
BMI, body mass index; AF, atrial fibrillation; CV, cardioversion; LA, left atrial; LV, left ventricular; sPAP, pulmonary artery systolic pressure. The significant *P*-values <0.05 are denoted in bold.

Figure 1



Receiving Operator Curve of septal E/e' ratio as predictor of AF recurrence at three months. A septal E/e' ratio ≥8 showed the best sensitivity (89%) and a septal E/e' ratio ≥11 the best specificity (85%). A septal E/e' ratio ≥11 presented the best diagnostic accuracy (AUC 0.66, 95% CI 0.55–0.76 *P* 0.007).

Figure 2



Receiving Operator Curve of the candidate predictors of AF recurrence at 3 months (LA volume, AF duration >90 days, septal E/e' ratio). The association of AF duration >90 days and septal E/e' ratio ≥11 in a 2-point score showed the best diagnostic accuracy (AUC 0.70, 95% CI 0.59–0.80, *P* 0.003).

Antiarrhythmic treatment and echocardiographic risk stratification

Before CV, 74 patients (58%) were treated with antiarrhythmic agents; after successful CV, the number of patients discharged on antiarrhythmic therapy increased to 99 (78%). Treatment did not show any significant protective effect on AF recurrence at 3 months as depicted in *Table 4*. Moreover, there was no significant difference in treatment prevalence between patients with and without E/e' ≥11 (respectively, 30/37 patients vs. 69/90 patients, *P* 0.17). E/e' ≥11 significantly predicted AF recurrence even when population was divided by presence/absence of treatment (respectively, *P* 0.032 and *P* 0.038). Analysing the risk of AF recurrence according to E/e' ≥11 and absence of therapy, we identified four different subgroups. Among patients with E/e' ≥11, those without therapy showed the highest incidence of AF recurrence (43%); the incidence decreased in the presence of therapy (37%). On the other hand, patients with E/e' <11 showed a slight effect of treatment on AF recurrence; AF recurrence was 27 and 23%, respectively, in patients with and without antiarrhythmic therapy.

Discussion

Our study is aimed to assess the role of LV diastolic dysfunction in predicting AF recurrence in a selected population of patients with moderate-to-severe LA dilation. Among all predefined parameters studied as risk factors of AF recurrence, a septal E/e' ratio ≥11, an easy and bedside echocardiographic marker of elevated LV filling pressure, is found to be the best predictor of early AF recurrence, together with the AF duration >90 days before the CV. It is well known that LV diastolic dysfunction could promote the AF onset and perpetuation, subjecting the left atrium to a pressure overload by long-term, which favours progressive

LA enlargement and electrical instability.[22] The septal E/e'ratio ≥11 is an index of elevated LV filling pressure (>15 mmHg) with a sensitivity of 75% and a specificity of 93% as demonstrated by Sohn *et al*.[12] Our data suggest that a septal E/e'ratio ≥11 could be also an independent predictor of early AF recurrence (OR 3.25 95% CI 1.19–8.86 *P* 0.001), with a specificity of 85%. This finding is in accordance with the previous study of Li *et al.*[7] that enrolled patients who underwent catheter ablation; in this population, the septal E/e' ratio ≥11 predicted AF recurrence at 3 months with a sensitivity of 80.8% and a specificity of 81.8%.

AF duration is a predictor of AF recurrence after CV.[23] According with this assumption, we found a greater risk of AF recurrence in patients with AF lasting more than 90 days before the recovery of SR (OR 2.69 95% CI 1.01–7.53 *P* 0.04), as reported by Ökçün *et al*.[17] So it is possible that in patients with moderate-to-severe LA dilation, the duration of AF, that is known to contribute to the atrial structural remodelling,[24] and a septal E/e ratio ≥11, expression of elevated LV filling pressure, were the main determinants that lead to AF recurrence.

A septal e' wave value <8 cm/s was an index of prolonged rate of myocardial relaxation in patients with AF as reported by Sohn *et al*.[12] We registered a lower septal e' in patients with AF recurrence at 3 months and using the prespecified cut off, patients with e' wave <8 cm/s had a risk of AF recurrence about three times greater with respect to patients who maintained the SR.

The pulmonary artery systolic pressure would seem to be related to a lower risk of AF recurrence (OR 0.86 95% CI 0.78–0.93 *P* 0.001). This result, although affected by the small size of the population, could be explained by the fact that patients with a higher pulmonary artery systolic pressure may be better treated with diuretic and vasodilatatory (RAAB) drugs and this could impact on AF recurrence by reducing LV filling pressure.

Previous finding of Shah *et al.*[25] demonstrated in a *post-hoc* analysis of AFFIRM study an association between concentric LV hypertrophy and increased AF recurrence. It is well known that a greater LV mass is associated to diastolic impairment. This could explain why LV hypertrophy predicted AF recurrence in the AFFIRM study. In our study, patients showed an increased LV mass (240.6 ± 83.4 g), nevertheless this parameter did not predict AF recurrence at multivariate analysis (OR 1.02 CI 95% 0.99–1.01 *P* 0.25). This could be explained by the fact that E/e' ratio performed better than LV mass in identifying patients with higher left-atrial pressure: LV hypertrophy predisposes to higher filling pressure, whereas E/e' ratio ≥11 actually identifies patients with higher filling pressure.

All these data show that diastolic dysfunction represents a quantifiable surrogate of the arrhythmogenic substrate for the AF recurrence in patients with moderate-to-severe LA dilation.

It is well known that the LA size is one of the main parameters that predict AF recurrence. Marchese *et al.*[5] reported in a study on patients with non-valvular AF who underwent successful CV that each mL/m^2 increase in LA index volume was independently associated with a 21% increase in the risk of AF recurrence (adjusted OR 1.21, CI 1.11–1.30, $P < 0.001$). Nevertheless, in our population, we did not notice a significant correlation between LA volume and AF recurrence. This result could be explained by the fact that we enrolled only patients with LA volume ≥34 mL/m^2, when the known[5] best discriminating LA volume value is 33.5 mL/m^2. In this setting, higher values failed in predicting the risk of AF recurrence. Apparently, when the atrial remodelling reaches such advanced stage, elevated LV filling pressure represents the driving factor in promoting AF.

In conclusion, in patients with persistent AF and moderate-to-severe LA enlargement, a septal E/e' ratio ≥11, marker of increased LV filling pressure, together with an AF duration more than 90 days, seems to predict early AF recurrence. This evidence, strengthened by the fact that septal E/e' ratio is an independent predictor of mortality,[26] confirms the need of a complete evaluation of diastolic function in AF patients. Moreover, in these patients at higher risk of AF recurrence and mortality, could be necessary provide the

restoration of SR as soon as possible. It would also be attractive to achieve a reduction of the septal E/e' ratio <11 cm/s before CV by improving medical therapy. Finally, our study suggested that not only patients with long lasting AF before CV but also patients with elevated septal E/e' ratio deserve antiarrhythmic treatment due to the high risk of AF recurrence. Besides AF ablation may become an attractive option in this subset of symptomatic patients with high echocardiographic risk of recurrence. Further studies are needed to demonstrate whether this strategy could help in managing this challenging population.

Study limitation

The present monocentric study was not part of a randomized trial. Moreover, it is acknowledged that echocardiographic methods are operator-dependent and require skill and experience. However, reproducible results may be achieved with a systematic core laboratory approach. Only 44 patients (34%) underwent TEE, therefore all data obtained by this examination should be used by caution. The same should be stated for atrial function analysis by 2D speckle tracking available for only 58 patients (46%). Finally, the follow-up was limited to 3 months. This short duration of the follow-up could have unmasked other clinical and echocardiographic predictors of AF recurrence.

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